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Cardiovascular autonomic evaluation and body fat analysis in COVID-19-recovered patients in Dakshina Kannada, India

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Abstract:

BACKGROUND: The pandemic, coronavirus disease 2019 (COVID-19) has led to a heavy toll on the human health. The aim of this study was to determine the influence of body fat distribution, evolving long-term effect on autonomic function, and its correlation with Chalder Fatigue Severity Score in post-COVID-19-recovered individuals of Indian ethnicity.

MATERIALS AND METHOD: A case–control study was conducted in the Department of Physiology on 31 cases and 29 age- and gender-matched controls. Cardiovascular evaluation including heart rate variability (HRV), galvanic skin response (GSR), body fat analysis, and Chalder Fatigue Severity Score was performed on the study participants. The continuous variables of basal anthropometric parameters, GSR values, HRV indices, and body fat parameters are expressed as mean and standard deviation (SD).

RESULTS: Diastolic blood pressure (DBP) was significantly increased among cases (P = 0.04). GSR (average) for cases is higher when compared to controls and was borderline significant (P = 0.05). There were no statistically significant differences in the HRV parameters. Cases showed significantly higher body fat distribution as compared to the control group indicating increased susceptibility of the obese population to COVID-19. Chalder's post-COVID-19 Fatigue Severity Score of cases showed a negative correlation with LF:HF and RMSSD but it was not statistically significant.

CONCLUSION: In our study, we conclude that there was a significant increase in DBP and GSR (average) with significantly higher visceral fat percentage, body fat percentage, subcutaneous fat percentage, skeletal muscle percentage, and trunk fat percentage in cases as compared to the control group suggestive of higher propensity of obese individuals suffering from COVID-19 and resulting in dysautonomia as compared to the controls.

Keywords:

Autonomic nervous system, COVID-19, obesity

Introduction

The fag end of the year 2019 changed and challenged the lifestyle of the entire world population due to an outbreak of respiratory infection which originated in Wuhan Hubei Province, China. This was labeled as coronavirus disease 2019 (COVID-19) and was declared as a pandemic respiratory syndrome on March 12, 2020. This COVID-19 pandemic led to a very high toll in terms of human lives lost.[1] The lockdowns imposed by the various governments along with economic repercussions affected the general lifestyle of the people. On the one end, people

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starved due to loss of livelihood; on the other end, they witnessed unhealthy eating behavior to cope with the pandemic stress leading to an imbalanced lifestyle. This pattern could have influenced the population at risk in India, warranting further exploration.[2] In addition, obesity is not only a risk factor for developing COVID-19 but also increases the severity of the disease.[3]

Reports of autonomic dysfunction with new-onset postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope, and orthostatic hypotension post-COVID-19 infection are emerging.[4] Deeper insights into the cardiovascular autonomic function through research will throw more light into the overall autonomic functioning of the human body.[5,6] Heart rate variability (HRV) and galvanic skin response (GSR) are a few of the investigations used to assess sympathovagal balance;[6-8] we planned to assess the autonomic functions by HRV and GSR.

Rate pressure product (RPP), is a derived index, calculated as a product of heart rate and systolic blood pressure (SBP), is a sensitive index for myocardial oxygen consumption in awake people.[9] The myocardial oxygen consumption post-COVID-19 has not been studied yet.

There also have been growing concerns of chronic fatigue syndrome in COVID-19-recovered patients resulting in long-term debility.[10] Moreover, the medical fraternity has opined the need for further research on this.[11] In this regard, there was a great need to assess the post-COVID-19 fatigue extent and severity using the Chalder Fatigue Scale (CFQ 11) and correlate the Fatigue Severity Score with the autonomic functions in COVID-19-recovered patients. The CFQ 11 has been used in studies testing for tiredness among working populations as well as patient groups. It has consistently fared extremely well against other longer complex tools.[12-14]

COVID-19 disease has claimed many lives in the last 2–3 years. Post-COVID-19 syndrome is an evolving symptomatology requiring more exploration with an indication toward autonomic/small-fiber dysfunction. Thus, the paucity of available literature hints at the need for early continued research on autonomic dysfunction following COVID-19 and may enable in providing initial insights into the spectrum of this condition as many of the survivors of this disease have started to develop long-term complications such as persistent fatigue and features of dysautonomia. As there are very few studies exploring the influence of cardiovascular autonomic status, body fat distribution, the severity of post-COVID-19 fatigue, and its correlation with the autonomic status among Indian ethnicity, we planned to determine the lifestyle and anthropometric parameters such as weight, body mass index (BMI), waist–hip ratio (WHR), body fat percentage, cardiovascular autonomic functions, and RPP in COVID-19-recovered patients; compare the same with the age-matched normal subjects; and also, correlate post-COVID-19 Fatigue Severity Score with their autonomic functions in COVID-19-recovered patients.

Materials and Methods

Study design and setting

A case–control study was conducted in the Department of Physiology of a Medical College Hospital, a unit of Deemed to be University, in Dakshina Kannada, Karnataka, India.

Study participants and sampling

Thirty-one (n1) COVID-19-recovered individuals, who were COVID-19-positive with real-time reverse transcription–polymerase chain reaction (RT-PCR) within the last 6 months, aged 18–45 years, working as teaching staff and undergraduate and postgraduate students of the same Deemed to be University in Dakshina Kannada, were considered as "cases" for the study thereby minimizing the detrimental effects of age on the autonomic functions. Twenty-nine (n2) age-matched healthy controls without documented past history of COVID-19 infection were considered as the controls. Individuals with documented autonomic dysfunction, those on medications known to affect the cardiovascular system such as sympatholytics, parasympathomimetics, sympathomimetics, and anticholinergics, and those with past history of COVID-19 infection >6-month duration were excluded from the study. The study was conducted between October 2021 and June 2022, during the second wave of COVID-19 infection in India. To avoid bias pertaining to different dominant strains of COVID-19 during a particular wave, only the second wave of COVID-19 infection was considered.

The sample size estimation was calculated by using G* power software for independent-sample *t*-test. At 95% level of confidence and standard effect size of 0.8 with 85% power, the minimum sample size in both the groups together was taken as 60 (cases + control).

Data collection tool and technique

Anthropometric measurements

Bodyweight and height were measured with participants standing erect without shoes in light clothes. Bodyweight was measured in kilograms to the nearest 0.1 kg using a digital scale, calibrated regularly. Height was measured to the nearest 5 mm using a stadiometer. BMI using Quetelet's formula, waist circumference, hip circumference, and WHR were determined. Waist circumference was measured at the end of several consecutive natural breaths, at a level parallel to the floor, and midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line. The hip circumference was measured at a level parallel to the floor and at the largest circumference of the buttocks. Those with BMI between 18.5 and 24.9 Kg/m^2 were considered as normal, between 25 and 29.9 Kg/m^2 were considered as overweight, and more than 30 Kg/m^2 were considered as obese. As per the World Health Organization (WHO) guidelines, abdominal obesity is defined as a WHR above 0.90.[15]

Body fat percentage

The body fat percentage was measured by a bioelectric impedance method by using an OMRON Body Composition Monitor (HBF-702 T) that measured the leg-to-hand resistance. It is manufactured by OMRON Healthcare from Japan. It is a lightweight handheld model. This is relatively simple, non-invasive technique to measure the body composition.[16] The body fat analyzer sends an extremely weak electrical current through the body to determine the amount of fat tissue. This weak electrical current is not felt while operating the body fat analyzer. The bioelectrical impedance method safely combined the electric resistance with the distance of the electricity conducted. The height, age, and gender of the subject were entered into the instrument. Each participant was instructed to hold the instrument in both the extended hands at right angles to the body after which the observer pressed the start button on the instrument, and the digital reading of the body fat percentage (total body fat %, fat in arms %, fat in legs %, and fat in trunk %),[17] visceral fat percentage, subcutaneous fat percentage, skeletal muscle percentage, and resting metabolism of the subject was recorded.

Autonomic function tests

Short-term HRV

Standard procedure was followed to record short-term HRV using Lead II ECG as per the recommendation of the task force. The data acquisition was performed using an ADInstruments PowerLab 8/35 Dual Bio Amp, N12128, Data Acquisition System (New South Wales, Australia). The sampling rate was kept at 500 samples/second per channel. HRV analysis of the RR tachogram was performed for time domain measures and frequency domain (by power spectral analysis using fast Fourier transformation). The frequency domain indices included low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.4 Hz), total power (TP), LF in normalized units (LFnu), HF in normalized units (HFnu), and the ratio of LF to HF (LF–HF ratio). Time domain measures included mean RR (mean of RR interval), standard deviation (SD) of RR interval (SDNN), the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 msec in the entire recording (NN50), and the percentage of NN50 counts, given by NN50 count divided by total number of all NN intervals (pNN50).[6]

Galvanic skin response

GSR was recorded using PowerLab 8/35 Data Acquisition System, and it measured the sweat resistance indicating changes in sweat gland activity thus reflecting the autonomic nervous system (ANS) regulation and functioning. The GSR values were recorded at 1, 2, and 3 minutes of rest, and the average of the values (GSR average) was taken. GSR value after stimulation using a standardized sound stimulus at the end of 5 minutes 30 seconds was also recorded (GSR stimulus). The difference between the two (GSR average minus GSR stimulus) is recorded as the GSR difference.

Basal cardiovascular parameters

Blood pressure (BP) was measured on the left arm, with an appropriately sized cuff, after at least 10 min of rest in sitting position, using a sphygmomanometer. The average of the last two measurements was used for the analysis according to the Joint National Committee 8 criteria.[18] RPP, an indirect measure of the myocardial oxygen consumption, was calculated as the product of heart rate and the SBP.

Fatigue Severity Scale

The extent and the severity of fatigue were measured using the Chalder Fatigue Scale, a self-administered questionnaire. It is a 11-item scale further divided into two components: one that measures physical fatigue (questions 1–7) and one that measures the mental fatigue (questions 8–11).[12,13]

Statistical analysis

Data were entered in Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 23. The continuous variables of basal anthropometric parameters, GSR values, HRV indices (time domain and frequency domain indices), and body fat parameters are expressed as mean and SD. A P value < 0.05 is considered as statistically significant.

Ethical consideration

This study was conducted after obtaining approval from the University Ethics Committee (Protocol No.: YEC1/2022/010). Written informed consent was obtained from each participant after describing in full detail the procedure and purpose of the study.

Results

Table 1 shows a significant difference in the diastolic blood pressure (DBP) among cases and controls.

GSR (average) for cases is higher when compared to controls and is borderline statistically significant [Table 2].

Table 3 shows no statistically significant difference in time domain indices of HRV between cases and control groups.

Table 4 shows no statistically significant difference in frequency domain indices of HRV between cases and control groups.

Cases showed a significantly higher visceral fat percentage, body fat percentage, subcutaneous fat percentage, skeletal muscle percentage, and trunk fat percentage in cases when compared to the control group [Table 5].

When Chalder's post-COVID-19 Fatigue Severity Score of cases was correlated with LF: HF and RMSSD, it showed Pearson's r of -0.01 (*P* value 0.97) and -0.08 (*P* value 0.67), respectively.

Table 1: Comparison of basal anthropometric and cardiovascular parameters between cases (n1=31) and control (n2=29) groups

Parameters	Groups	Mean	Std. deviation	*P*
Weight (Kg)	Cases	61.67	11.49	0.83
	Controls	62.34	11.56	
WHR	Cases	0.80	0.07	0.23
	Controls	0.77	0.08	
BMI (Kg/m^2)	Cases	24.18	3.47	0.85
	Controls	24.37	4.15	
SBP (mm Hg)	Cases	105.16	10.05	0.54
	Controls	106.71	10.11	
DBP (mm Hg)	Cases	70.44	7.92	0.04
	Controls	66.00	8.39	
HR (beats/min)	Cases	77.16	10.95	0.52
	Controls	75.21	12.46	
RPP	Cases	8122.16	1489.28	0.71
	Controls	7988.07	1256.77	

Values are expressed as mean±SD. Analysis was conducted by unpaired *t*-test. WHR—waist–hip ratio; BMI—body mass index; SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate; RPP—rate pressure product

Table 2: Comparison of GSR parameters between cases (n1=31) and control (n2=29) groups

Parameters	Groups	Mean	Std. deviation	*P*
GSR (stimulus) μS/cm	Cases	0.23	0.28	0.33
	Controls	0.18	0.11	
GSR (average) μS/cm	Cases	-0.0085	0.06	0.05
	Controls	-0.033	0.03	
GSR (difference) μS/cm	Cases	0.24	0.29	0.60
	Cases	0.21	0.11	
	Controls	0.93	0.78	

Values are expressed as mean±SD. Analysis was conducted by unpaired *t*-test. GSR—galvanic skin response

Table 3: Comparison of time domain indices of HRV between cases (n1=31) and control (n2=29) groups

Parameters	Groups	Mean	Std. deviation	*P*
SDNN (ms)	Cases	55.13	31.23	0.84
	Controls	56.55	19.95	
Mean HR	Cases	76.92	9.725	0.35
	Controls	74.67	8.78	
RMSSD (ms)	Cases	54.34	46.95	0.92
	Controls	55.29	21.56	
pNN50	Cases	24.98	25.45	0.50
	Controls	28.64	15.58	

Values are expressed as mean±SD. Analysis was conducted by unpaired *t*-test. SDNN—standard deviation of NN intervals; mean HR—mean heart rate; RMSSD—square root of the mean squared differences of successive NN intervals; pNN50—percentage of NN50.

Discussion

To the best of our knowledge, this is among the first few studies conducted for the cardiovascular autonomic evaluation including GSR and body fat analysis on COVID-19-recovered South Indian individuals. We found that there was a significant increase in DBP among cases [Table 1] as compared to the controls. Aranyó J *et al*.,[19] in their scientific findings, have reported an inappropriate sinus tachycardia following post-COVID-19 syndrome and have suggested that the loss of HRV indicates cardiac ANS imbalance with decreased parasympathetic activity and compensatory sympathetic activation. Thus, increased DBP in our study can be attributed to increased sympathetic activation. In addition, our study found that the GSR (average) for cases was borderline significantly higher than that of the controls [Table 2]. This finding further adds on to the evidence of dysautonomia with sympathetic dominance in the cases. GSR evaluation is a simple way of testing the autonomic function that though easily feasible has hardly been conducted elsewhere. It has been postulated that the dysautonomia might be mediated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus itself and/or due to oxidative stress following the cytokine storm. Mediators of inflammation can probably cross the blood–brain barrier and directly stimulate the central sympathetic centers.[20] However, in contrast to the study by Aranyó J *et al*.[19], we did not find any significant reduction in the HRV parameters [Tables 3 and 4]. This difference probably stems from the fact that we performed a short-term HRV recording. Hence, there is a need to further explore, compare, and contrast the utility of short-term versus long-term HRV monitoring to gauge the dysautonomia in post-COVID-19-recovered patients. RPP, an indicator of myocardial oxygen consumption in awake subjects, was not significantly different among cases and controls implying no much changes in the coronary supply to the myocardium.

On determining an association between the bioelectric impedance analysis of body composition and the cases of COVID-19-recovered participants, we found

Table 4: Comparison of frequency domain indices of HRV between cases (n1=31) and control (n2=29) groups

Parameters	Groups	Mean	Std. deviation	*P*
TP	Cases	2946.03	3116.81	0.60
	Controls	2593.54	1880.14	
VLF	Cases	689.53	520.74	0.57
	Controls	787.07	794.78	
LF	Cases	782.47	954.50	0.75
	Controls	717.30	552.41	
HF	Cases	1399.88	1999.13	0.40
	Controls	1059.16	809.14	
LF (nu)	Cases	42.35	18.91	0.96
	Controls	42.59	15.79	
HF (nu)	Cases	57.00	18.20	0.81
	Controls	55.94	15.17	
LF/HF ratio	Cases	1.04	1.18	0.68
	Controls	0.93	0.78	

Values are expressed as mean±SD. Analysis was conducted by unpaired *t*-test. TP—total power; LF—low frequency; HF—high frequency; (nu)—normalized units; VLF—very low frequency

Table 5: Comparison of frequency domain indices of HRV between cases (n1=31) and control (n2=29) groups

Parameters	Groups	Mean	Std. deviation	*P*
Visceral fat	Cases	6.66	4.16	0.004
	Controls	4.11	2.04	
BMI	Cases	24.18	3.47	0.85
	Controls	24.37	4.14	
Body fat%	Cases	31.24	4.77	0.003
	Controls	27.49	4.55	
Subcutaneous fat%	Cases	25.83	5.69	0.021
	Controls	22.51	4.99	
Skeletal muscle%	Cases	26.52	3.30	0.045
	Controls	24.86	2.93	
Resting metabolism	Cases	1323.63	205.59	0.480
	Controls	1286.36	198.81	
Arm fat%	Cases	40.67	8.76	0.121
	Controls	37.13	8.65	
Trunk fat%	Cases	22.53	5.20	0.010
	Controls	19.17	4.47	
Leg fat%	Cases	37.33	7.47	0.085
	Controls	33.99	7.19	

Values are expressed as mean±SD. Analysis was conducted by unpaired *t*-test. BMI—body mass index

significantly high visceral fat percentage, body fat percentage, subcutaneous fat percentage, skeletal muscle percentage, and trunk fat percentage among the cases as compared to the control group [Table 5]. Though there are many studies correlating BMI with the severity of COVID-19, not many studies exist on the *per se* association of the subcutaneous and trunk fat percentage with COVID-19. In line with our findings, Min Gao *et al*.,[21] in their prospective, community-based cohort study, found a linear increase in BMI and the risk of severe COVID-19 enhancing risk of hospital admission and mortality in population belonging to < 40 years of age. Obesity itself can induce a persistent low-grade inflammatory process in the body ultimately compounding to the cytokine storm occurring during COVID-19 thus precipitating increased severity of the disease process.[22] However, Moonen *et al*.,[23] in their study, did not find any association between disease severity and body composition, including fat mass, visceral fat area, and fat-free mass among the cases admitted in the ward versus the intensive care unit (ICU). This could be attributed to the fact that all the participants in their study belonged to the overweight category and lacked a control arm. Also, this highlights the fact that there are probably differences in the outcomes post-COVID-19 owing to difference in ethnicities. The type of body fat distribution varied among ethnicity, and hence, there arises the need for large-scale studies on different ethnicities and COVID-19 outcomes in terms of dysautonomia. In contrast, Battisti *et al*.[24] in their study of COVID-19 patients with adverse outcomes documented an excess visceral fat accumulation as measured by computed tomography (CT). Our study was able to find similar association with simple bioimpedance studies of body fat percentage and risk of COVID-19 and thus can be part of the battery of investigations in resource-constrained settings.

Our finding underlines the importance of thorough longitudinal evaluation of COVID-19-recovered individuals even if they are young and did not experience severe clinical symptoms requiring hospital admissions as the dysautonomia revealed can have long-term implications adding to the severity of the burden of non-communicable diseases given the pandemic proportion of COVID-19.

Vimercati *et al*.[25] found that being overweight and obese precipitates long COVID syndrome characterized by the persistence of symptoms resulting in reduced work performance among healthcare workers. When we assessed Chalder's post-COVID-19 Fatigue Severity Score of the cases with the indicators of sympathetic overactivity, though there was a negative correlation, it was not statistically significant [Figures 1 and 2]. A systematic review by Joli J *et al*.[26] revealed that the potential risk factors for post-COVID-19 fatigue included old age and severity of infection. On the contrary, our participants belonged to the 18- to 45-year age-group and none of the cases had experienced severe clinical status during the acute phase of COVID-19 infection.

Limitation and recommendations

The most important limitation of our study was the small sample size (N = 60) though we had a case–control study design. This is of main concern because the HRV measures are very subjective and highly variable. There is a continued need for the longitudinal follow-up

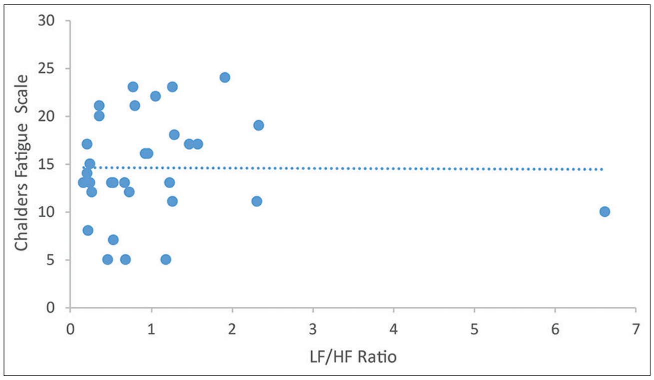

Figure 1: Pearson's correlation of Chalder Fatigue Severity Score with LF/HF ratio [Pearson's r of -0.01 (*P* value 0.97)]

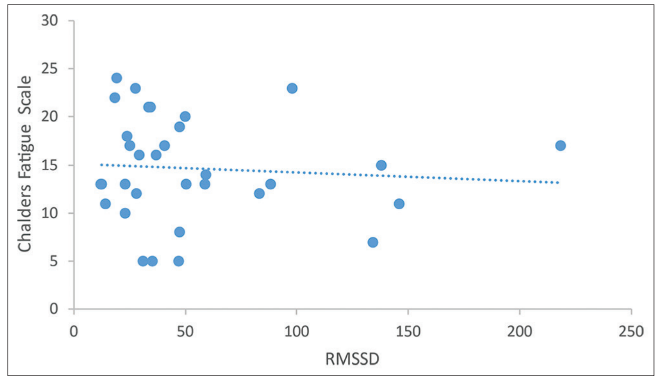

Figure 2: Pearson's correlation of Chalder Fatigue Severity Score with RMSSD [Pearson's r of -0.08 (*P* value 0.67)]

of the same study group for concrete evaluation of the long-term evolution of dysautonomia following COVID-19. At the same time, our study also presents many strengths. Even though India contributed in a big way to the number of cases of the pandemic, given it being the second most populous country in the world, not many Indian studies were conducted to evaluate the cardiovascular autonomic consequences and the impact of body fat percentage on COVID-19. Also, our study allows for further exploration of the clinical utility of GSR measurement as a simple and feasible measure of autonomic function following COVID-19. Given the undoubted association between various body fat distribution and the cases of COVID-19 as revealed by our study, there is a need for further molecular studies to reveal the pathophysiological signaling pathways involved in precipitating the COVID-19 symptoms in obese individuals of Indian ethnicity.

Conclusion

The COVID-19 pandemic is an ongoing global health crisis that affects multiple organ system in our body. In this study, an attempt was made to determine the anthropometric parameters such as weight, BMI, WHR, body fat percentage, cardiovascular autonomic functions, and RPP in COVID-19-recovered patients; compare the same with the age-matched normal subjects; and correlate post-COVID-19 Fatigue Severity Score with their autonomic functions in COVID-19-recovered patients. Our results showed that there was a significant increase in DBP and GSR among COVID-19-recovered patients compared to the normal subjects of Indian ethnicity. The visceral fat percentage, body fat percentage, subcutaneous fat percentage, skeletal muscle percentage, and trunk fat percentage were significantly higher in COVID-19-recovered patients compared to the normal subjects. The Fatigue Severity Score among post-COVID-19 patients showed a negative correlation though not significant, with LF: HF and RMSSD values. The study warrants further large-scale population-based studies to explore dysautonomia following COVID-19 among the Indian ethnicity.

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Conflicts of interest

There are no conflicts of interest.

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